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09/744,654	01/29/2001	Tsvee Lapidot	LAPIDO2	2645

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,654	Applicant(s) Lapidot
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 10, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 10-21, 23-27, 33, 48, 49, and 53-116* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 10-21, 23-27, 33, 48, 49, and 53-116* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response received on 4/10/03 has been entered. Claims 2, 6-9, 22, 28-32, 34-47 and 50-52 have been canceled. New claims 53-116 have been entered. Claims 1, 3-5, 10-21, 23-27, 33, 48-49, and 53-116 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, not included in this office action can be found in the previous office action.

Claim Rejections - 35 USC § 102

Applicant's amendments and addition of new claims have necessitated the following new grounds of rejection.

Claims 80-81, 83-94, 96-106, 108-116 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Viardot et al. (1997) Blood, Vol. 10 Suppl. 1 part 1, page 478. The applicant claims pluripotent human hematopoietic CD38-/low CXCR4+ stem cells capable of migrating in response to SDF-1 or capable of adhering to stromal cells in response to the adhesion inducing agent SDF-1. The applicant further claims said cells which are CD34+. Please note that independent claims 80, 92, and 105 recite wherein the cells are selected from a group consisting of CD38-/low cells that express CXCR4 on the cell surface and cells which are CD38-/low

CXCR4-/low cells which can be converted to CD38-/low CXCR4+ cells by stimulation with an agent. Dependant claims recite limitations which relate to suitable agents for stimulating the second set of CD38-/low CXCR4-/low cells. However, all the claims read on cells which are either CD38-/low CXCR4+ or CD38-/low CXCR4-/low. Therefore, all the recited claims read on CD38-/low CXCR4+ human hematopoietic stem cells.

Viardot et al. teaches a cell population with is CD34+ CXCR4+ CD38low CD33dim, which the authors identify as human hematopoietic stem cells (Viardot et al., abstract 2126). Viardot et al. further teaches that these cells represent more immature cells that those that express CD34+ and CD38+ or CD33+ (Viardot et al., abstract). In addition, Viardot et al. teaches that the natural ligand of CXCR4 is SDF-1 and states that CXCR4 can play a role in homing of immature CD34+ to stromal elements in the bone marrow (Viardot et al. abstract).

Regarding the language " capable of migrating in response to SDF-1 and capable of adhering to stromal cells in response to an adhesion inducing agent, such as SDF-1, please note that the claims as written are product claims, claims 80-104, or product by process claims, claims 105-106, 108-116. The applicant is reminded that, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). The MPEP further states that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP

211.01 and *In re Best*, 195 USPQ 430, 433 (CCPA 1997). In addition, "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990). Specifically in regards to the product by process claims, the MPEP states that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Finally, the applicant is reminded that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Therefore, by teaching cells which have the same structure as the cells recited in the claims, Viardot et al. anticipates the claims as written.

The rejection of claims 1-14 under 35 U.S.C. 102(a) as being anticipated by Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530, is maintained over original, amended, or new claims 1, 3-14, 53-64, and 80-116. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of reasons of record as discussed in detail below.

Applicant's claims as amended recite pluripotent human hematopoietic CD38-/low CXCR4+ stem cells capable of migrating in response to SDF-1 or capable of adhering to stromal cells in response to the adhesion inducing agent SDF-1. The applicant further claims said cells which are CD34+. The applicant also claims cell compositions consisting essentially of CXCR4+ CD38-/low human hematopoietic stem cells capable of migrating in response to SDF-1 and/or capable of adhering to stromal cells in response to an adhesion-inducing agent such as SDF-1. The applicant further claims said compositions wherein the cells are CD38 low, CD34- /CD38 low, CD34+/CD38low, or CD38+. Please note that independent claims 1, 80, 92, and 105 recite wherein the cells are selected from a group consisting of CD38-/low cells that express CXCR4 on the cell surface and cells which are CD38-/low CXCR4-/low cells which can be converted to CD38-/low CXCR4+ cells by stimulation with an agent. Dependant claims recite limitations which relate to suitable agents for stimulating the second set of CD38-/low CXCR4-/low cells. However, all the claims read on cells which are either CD38-/low CXCR4+ or CD38-/low CXCR4-/low. Therefore, all the recited claims read on CD38-/low CXCR4+ human hematopoietic stem cells.

The previous office action cited Mohle et al. for teaching purified compositions of cells, including CD34 -cells, CD34+ cells, CD34+/CD38low cells, CD38+ cells, and CD38low cells, all of which express CXCR4 and migrate in response to SDF-1 (Mohle et al., pages 4525-4527, and Figures 1-3). Mohle et al. further teaches human CXCR4+ cells derived patient's peripheral blood, which can be considered either autologous or allogeneic. Mohle et al. also teaches populations of cells wherein the majority of cells express CXCR4 and a subpopulation is CXCR4-/low (Mohle et al, page 4526, Figure 2).

The applicant argues that the cell populations taught by Mohle et al. are not capable of migrating to, and of engraftment and repopulation of, the bone marrow in a host. The applicant states that migration and engraftment are not inherent features of CXCR4 cells which migrate in response to SDF-1 and that the cells taught by Mohle are not stem cells because they were found in the peripheral blood and not in the bone marrow. In response, the cell populations taught by Mohle et al. which express CXCR4 include CD34+ CD38 low cells and CD34-CD38 low cells. Mohle et al. further teaches that primitive hematopoietic cells capable of hematopoietic reconstitution are CD38 low CD34+ cells which further have a CD45RA low, Thy-1+, and HLA-DR low phenotype (Mohle et al., page 4527-4528). In addition, please note that applicant's claims 10, 57, 83, 96, and 108 all recite wherein the cells are derived from mobilized peripheral blood. Thus, applicant's argument that cells found in peripheral blood are not stem cells conflicts with the invention as claimed, and is refuted by the specific teachings of Mohle et al.

In addition, regarding the language " capable of migrating in response to SDF-1", "capable of adhering to stromal cells in response to an adhesion inducing agent", such as SDF-1, and "having the capacity of migrating to, and of engraftment and repopulation of, the bone marrow in a host", please note that the claims as written are product claims, or product by process claims. As stated in the previous office action, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). The MPEP further states that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP 211.01 and *In re Best*, 195 USPQ 430, 433 (CCPA 1997). In addition, "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990). Specifically in regards to the product by process claims, the MPEP states that "[E]ven though product -by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Finally, the applicant is reminded that the office does not have the facilities for

examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Applicant's statement that the cells disclosed by Mohle are not capable of hematopoietic reconstitution of bone marrow does not meet the burden for demonstrating the claimed products are functionally different than those taught by the prior art and to establish patentable differences. The MPEP states that the arguments of counsel cannot take the place of evidence in the record . *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965). The applicant has not provided any specific evidence that the CD34+ CD38 low CXCR4+ cells taught by Mohle et al. cannot engraft in a host. Further, the evidence of record, as represented by prior art references made of record in applicant's IDS filed on 1/29/01 clearly teaches that CD34+CD38- cells are capable of long term engraftment in both primary and secondary recipients, see for instance reference AG, Zanjani et al., page 353, column 2). Therefore, applicant's arguments are not compelling in the absence of specific evidence which demonstrates that the CD34+ CD38 low CXCR4+ cells taught by Mohle et al. cannot engraft in a host.

Thus, by teaching cells populations with a structure identical to that recited in the claims, Mohle et al. anticipates the claims as written.

Claim Rejections - 35 USC § 103

The rejection of claims 15-27, 33, and 48-49 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,541,103, 7/30/96, hereafter referred to as Kanz et al. in view of Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530, is maintained over original, amended, or new claims 15-21, 23-27, 33, 48-49, and 65-79. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant claims methods of increasing the population of human hematopoietic stem cells for use in clinical transplantation comprising up-regulating surface CXCR4 expression and sorting out those CXCR4 stem cells that migrate in response to SDF-1. The applicant further claims said methods wherein CXCR4 is up-regulated by stimulation with cytokines such as IL-6 and SCF, or stromal cells, or stomal cells and a mixture of SCF and IL-6. The applicant further claims methods of screening for cells suitable for transplantation comprising the stimulation of cells with IL-6 and SCF followed by sorting of the cells for SDF-1 responsiveness by carrying out an in vitro transmigration assay across a mechanical barrier of cells wherein the cells to be sorted are the cells which transmigrate in response to SDF-1. Please note that the intended use of the

instant methods for preparing cells "for clinical transplantation" recited in the preamble does not constitute a step in the methods as claimed. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In re Hirao , 535 F.2d 67, 190 USPQ 15 (CCPA 1976); Kropa v. Robie , 88 USPQ 478, 481 (CCPA 1951).

The applicant argues that Kanz et al. teaches that treatment of human peripheral blood CD34+ cells with IL-6 and SCF-1 results in expansion of the cells, whereas the instant invention involves increasing the number of cells in a population that express CXCR4 without expansion. The applicant further argues that the instant invention incubates the cells for a short period, up to 5 days, and no the 3-4 weeks taught by Kanz et al. In response to applicant's argument that Kanz fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., upregulation of CXCR4 without cell expansion, and periods of cell incubation with stimulating agents) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The applicant further argues that neither Kanz et al. nor Mohle et al. teach stem cells. The applicant has not actually provided any specific arguments or evidence which demonstrates that the cells taught by Kanz et al. are not stem cells. In regards to Mohle et al., applicant's arguments have been addressed in detail above and have not been found compelling in view of the structure

of the cells taught by Mohle et al., CD34+CD38low CXCR4+, and the state of the art of pluripotent hematopoietic stem cells at the time of filing. Therefore, the rejection of record is maintained.

Claim Rejections - 35 USC § 112

The rejection of claims 7-9 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's cancellation of the claims.

Applicant's amendment has necessitated the following new grounds of rejection of the claims.

Claims 1, 3-5, 10-14, 53-64, and 80-104 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims have been amended to recite whether in the human CD38 -/low CXCR4+ hematopoietic stem cell or cell composition consisting essentially of CD38-/low CXCR4+ stem cells are selected from a group which includes CXCR4-/low stem cells that , "have the potential to express CXCR4 on the cell surface". It is unclear how cells which are CXCR4-/low meet the initial claim limitation of cells which are CXCR4+. The claims are product claims and not method claims. While the claim indicates that the CXCR4-/low cells can be stimulated to express CXCR4, a cell which has the "potential" to express CXCR4 is

not the same as a cell which actually expresses CXCR4 and is considered CXCR4+. As such, the claims are confusing in that it is unclear which cell population the applicant wishes to claim, CD38-/low CXCR4+ cells or CD38-/low CXCR4-/low cells. Therefore, the metes and bounds of the claims cannot be determined.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER